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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under 37 CFR 1.53 (b)(2).

Docket Number	26518	Type a plus sign (+) inside this box ->	+

INVENTOR(s) / APPLICANT(s)

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TITLE

ALBUMIN MADE DEVICES, MEDICAL IMPLANTS AND METHODS OF MAKING AND USING THEM

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification	*Number of Pages*	6	☑ Applicant is a Small Entity	
☑ Drawing(s)	*Number of Sheets*	2	☑ Other (specify) 3 claims	Assignment

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☐ A check or money order is enclosed to cover the filing fees		FILING FEE AMOUNT ($)	$ 80.00
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No

☐ Yes, the name of the US Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE _____ Date October 19, 2003

TYPED or PRINTED NAME SOL SHEINBEIN

25,457
REGISTRATION NO.
(if appropriate)

☐ Additional inventors are being named on separately numbered sheets attached hereto

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

ALBUMIN MADE DEVICES, MEDICAL IMPLANTS AND METHODS OF MAKING AND USING THEM

Inventors: Irena WASSERMAN, Michael DROR and David SIMHONI

Introduction

Implanted devices that are biocompatible and bioresorbable have been of interest for a long time. One specific example relates to sleeves or hollow tubes of a small diameter that the surgeon places in the body. Sleeves of this nature could be used as scaffoldings while repairing a cut in the intestines. An alternative use is the creation of an anastomosis of a severed member like a nerve. The ends need to be held in proximity for a finite amount of time to effect healing. To date there are no satisfactory products of this nature.

The challenge of creating a sutureless vascular anastomosis has been described recently[1]. The technologies include:

- Rings[2]
- Staples[3] and clips[4]
- Adhesives[5,6]
- Tubes[7] and stents[8]

To date, none of the above has proven satisfactory. Of special mention are the absorbable fibrin tubes[7] and the soluble triglyceride based stents[8]. The fibrin devices were prepared from fibrinogen and thrombin. The products were unsatisfactory due to issues of antigenicity and anaphylaxis.

Albumin based stents have been described in the literature[9]. These devices were brittle upon drying most probably due to the lack of plasticizers addition. In the present study we are describing albumin stents and sleeves that retained flexibility when dry and retained mechanical properties for a significant period prior to being resorbed in physiological fluids.

Experimental Details

Materials:

Albumin - Bovine serum albumin solid powder purchased from ICN (Cat # 160069)
Glycerol – Analytical grade; purchased from Frutarom (Cat # 551190)
Pentaerythritol – Analytical grade; purchased from Aldrich Chemicals (Cat # P475-5)

Methods:

Preparation of albumin sleeves consisted of 3 steps:

*Film casting

*Shaping of tubes
*Thermal curing

Films were cast from aqueous solutions of albumin and the required plasticizers. Typical ratio of albumin to plasticizers was 3:1 (W/W) and various other ratios were experimented with. The typical concentration of albumin in water was 30 % (W/W). The solution was cast on an adequate substrate so as to form a film that could then be easily peeled off. The substrate was leveled so as to obtain a film of uniform thickness. The drying process was typically carried out in an enclosure like a dessicator in the presence of a drying agent like silica gel. Special precautions were taken to avoid the formation of air bubbles that could be the source of imperfections in the film. The thickness of the films was a function of the volume that was cast as well as the shape of the mold and the concentration of the solution. Various plasticizers were tested and todate the best results were obtained with glycerol. Some experimentation is on going using mixed plasticizers like glycerol: pentaerythritol (9:1 ; W/W)

Tubes were prepared from dry films that were rewetted shortly before wrapping them around a cylinder of glass or other appropriate material of the desired dimensions. The ID (inner diameter) of the tube (OD of the cylinder) ranged between 1 mm and 3 mm. Drying was accomplished while the albumin was on the mold. The dried tube was then pulled off the mold.

Curing was an essential step in order to obtain the desired properties of the final product. Thus various temperature and time combinations were attempted. Moreover it was found that the best results were obtained while the heated film contained some residual amount of water that was typically in the range of 10-15% of the net weight of the film. The heating was performed in a high humidity environment at a temperature range of 60 – 85 deg C while the heating duration ranged between 10 – 60 mins.

Experimental Results

Characterization of cured albumin samples was performed initially in vitro by testing water absorption and weight loss during immersion. These tests were performed in saline (0.9% saline) at 37 C. A series of identical samples was immersed and pulled out at different time points from the immersion tank. The samples were wiped, weighed and then dried to constant weight. In this way it was possible to determine both weight loss and water absorption. It was found that samples that were cured after completely removing all traces of water (by drying to constant weight), totally dissolved in saline after several hours. The results of water absorption by samples containing 10-13% water that were cured at different condition are shown in Fig. #1. It is clearly seen that the higher the curing temperature, the lower the water uptake capability of the albumin matrix. Also, most of the water uptake occurs in the first 20 mins.

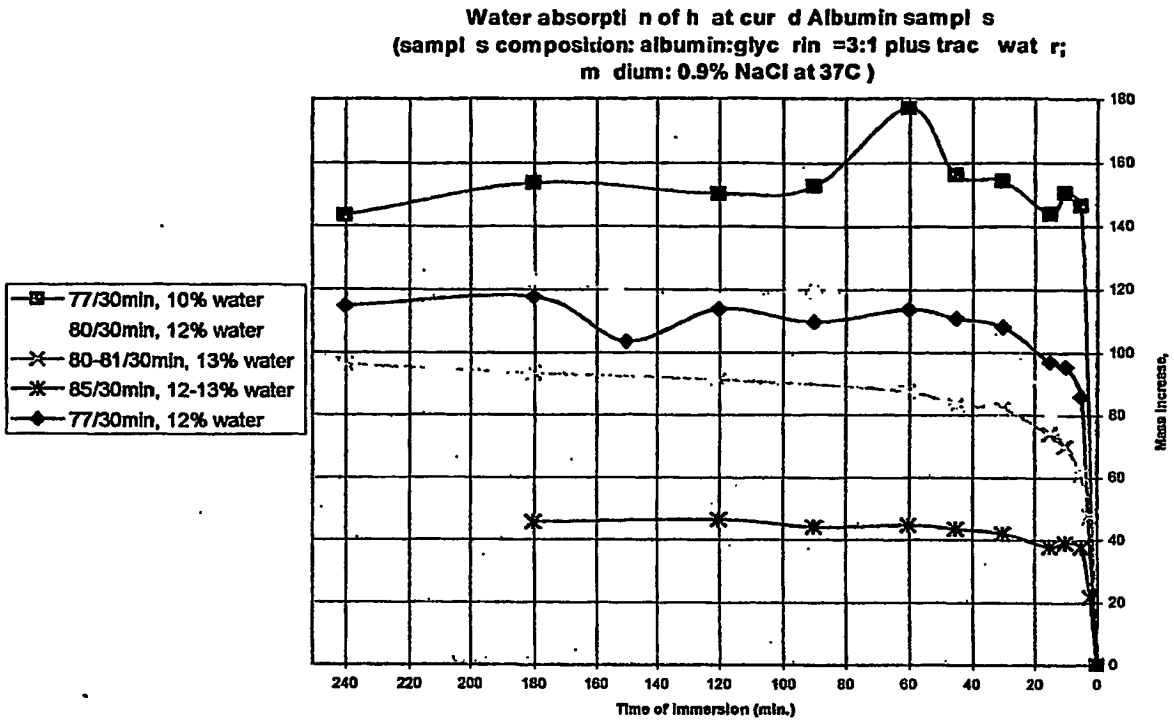

Figure 1: Mass increase (%) as a function on Time during swelling

Dissolution rate of the cured albumin samples in saline as a function of time is depicted in Figure 2.

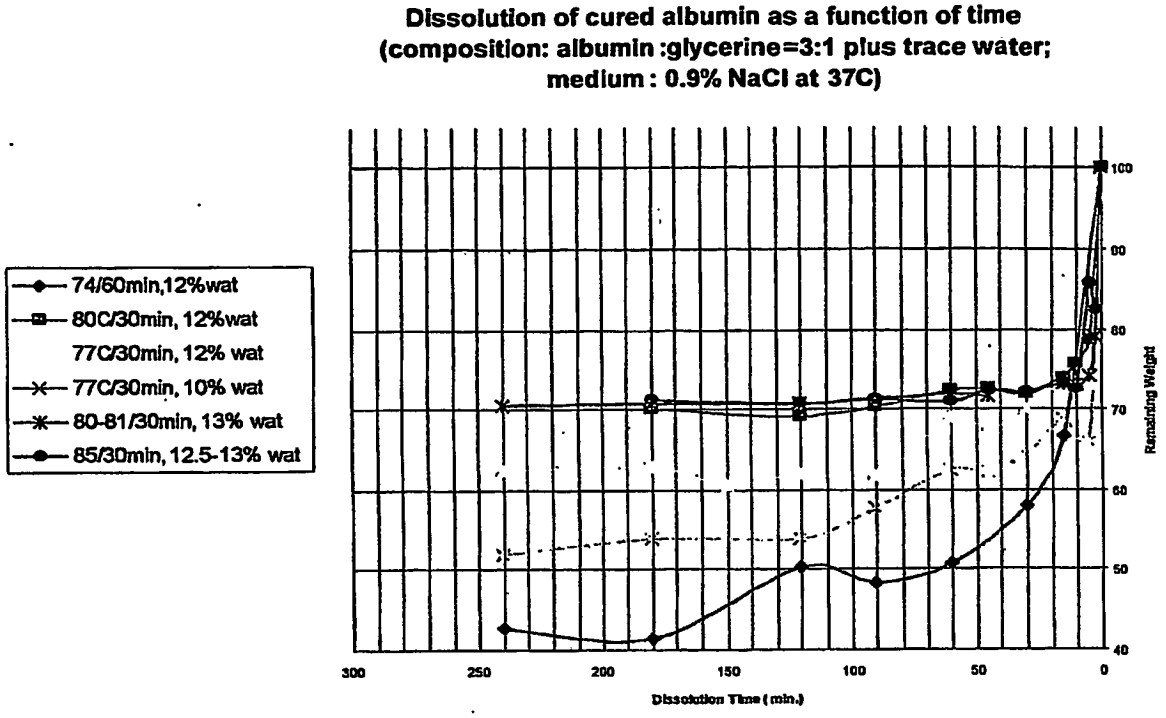

Figure 2: Remaining weight (%) as a function of time during immersion

The initial weight loss is most likely a result of glycerine diffusing out of the sample. Samples that were heated to temperatures lower than 80 C show also dissolution of some of the albumin matrix. Most of the dissolution in saline occurs in the initial two to three hours.

Animal studies carried out on rat and rabbit models demonstrated that albumin sleeves prepared using the new technology maintain adequate mechanical properties during surgery and are resorbable in the time range of 24-48 hrs. This means that a sleeve that is placed by the surgeon in the intestines provides adequate mechanical support to the vessel walls for at least several hours. At the same time, this sleeve is also resorbed in a time period that depends to the curing conditions. It appears that some proteolytic enzymes are responsible for dissolution of samples that remained intact in saline.

Discussion

Heat curing of albumin films and objects may change the solubility and water uptake properties of albumin. Clearly there is no change in properties when the heated sample is completely dry. This suggests that traces of water are catalyzing the process that results in lowering of solubility and lowering of water uptake. It is our belief that the process is one of secondary denaturation that is not reversible. So far we have no evidence to suggest that formation of covalent crosslinks has occurred as a result of the curing.

It is seen from our data that the higher the curing temperature and the longer the duration of curing, the lower the solubility and the lower the interaction with water. While the solubility is decreasing, also the water uptake or swelling decreases. These 2 properties are highly significant for the application of devices made by this novel process. The data shows that with this process we have the ability to engineer and design the desired properties of the albumin device.

The samples that demonstrate reduced swelling are also less flexible and when implanted retain mechanical strength for a longer time. The plasticizer diffuses out of the device and we believe that it enables enzymes to penetrate the matrix thus taking part in a slow degradation and resorption. The fact that samples that did not dissolve in saline at physiologic conditions, did disappear after 24 hrs in animal studies supports our hypothesis.

The results obtained to date demonstrate our ability to engineer the properties of the devices through judicious choice of the following:

1) Composition and concentration of plasticizers
2) Curing temperature and duration
3) Percent of water in the cured sample
4) Humidity of the environment during curing

It is our belief that this novel technology may be used for the production of a wide range of devices. The method of production are not limited to that described in the experimental section above. Stents and sleeves can be produced by injection molding and by extrusion. Films can be fabricated by calendaring and by compression molding. Rotational molding and spin casting are powerful techniques that appropriate for certain devices. Thus all the technology that is available for plastomers and elastomers is also applicable for the devices at hand in this paper.

Examples of albumin devices and their applications include the following list which is not intended to be limiting:

Stents

Scaffold for intraluminal end to end anastomoses:
Gastrointestinal anastomoses.

Vascular surgery.
Transplantations (heart, kidneys, pancreas, lungs)
Pulmonary airways (trachea, lungs etc.)

Laser bonding or other tissue type bonding (sutures, clips, glues, no mechanical approximating device)
Cardiovascular stents (using the swelling ability of the new stents)
Supporting stents for keeping body orifices open

Sleeves

With or without intraluminal stents.
Outside scaffold for nerves and tendons anastomoses (suturless and non sutureless)

Films

Protective and reinforcing films (for laser bonding or other glues)
Biodegradable wound dressing
Substrate for cell culturing
Prevention of adhesions
Abdominal wall surgical reinforcement

Glues

Reinforced glue for laser bonding
Reinforced sealants (as additives to the new Bioglue)

Medication

Additive to antibiotics
Additive to tissue growth factors
Additive to antiaggregants (anti clot forming substances)

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Claims:

1. An albumin made device essentially as described and exemplified herein.
2. A method of making an albumin made device essentially as described and exemplified herein.
3. A use of an albumin made device essentially as described and exemplified herein.